

# Measurement of Fraction of Exhaled Nitric Oxide With the Portable NIOX-MINO Monitor in Healthy Adults

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Measurement of the fraction of exhaled nitric oxide ( $FE_{NO}$ ) provides a noninvasive way to monitor asthma treatment in clinical practice. The aim of this study was to determine  $FE_{NO}$  reference values for measurements recorded with the portable NIOX MINO monitor in a group of healthy volunteers. We also assessed the association between values recorded by the portable monitor and the N-6008 chemiluminescence analyzer used in our pulmonary function laboratory. The  $FE_{NO}$  values obtained with the portable monitor were consistently higher than those recorded by the N-6008 monitor; the cutoff value for the portable monitor was 34 ppb (mean + 2 SD). We detected a direct correlation ( $r=0.92$ ) between the  $FE_{NO}$  measurements recorded by the 2 monitors ( $P=.001$ ). The following equation expresses the relationship between measurements from the 2 devices:  $FE_{NO}(NIOX-MINO) = 10 + [1.5 FE_{NO}(N-6008)]$ . We did not observe statistically significant correlations between  $FE_{NO}$  measurements and age, sex, body mass index, or spirometry.

**Key words:** Fraction of exhaled nitric oxide. Asthma. Inflammation.

Determinación de óxido nítrico en aire espirado ( $FE_{NO}$ ) mediante un equipo portátil (NIOX-MINO® Aerocrine) en población sana

La determinación de óxido nítrico en aire espirado ( $FE_{NO}$ ) es una técnica no invasiva que se utiliza en la evaluación clínica y el tratamiento del asma. El objetivo de este estudio ha sido determinar los valores de referencia de  $FE_{NO}$  en un grupo de voluntarios sanos mediante la utilización de un nuevo equipo portátil (NIOX-MINO® Aerocrine), así como determinar el grado de relación que presenta con el equipo de determinación habitual en nuestro laboratorio de función pulmonar (sensor de quimioluminiscencia N-6008® SIR). Según los resultados obtenidos, los valores de  $FE_{NO}$  que da el equipo portátil son siempre superiores a los que ofrece el sensor habitual, con un valor de corte de 34 ppb (media + 2 desviación estándar). Existe un relación directa y significativa de la determinación de  $FE_{NO}$  entre ambos equipos ( $r = 0,92$ ;  $p = 0,001$ ) con un factor de corrección de:  $FE_{NO}(NIOX-MINO®) = 10 + 1,5 FE_{NO}(N-6008®)$ . La relación entre los valores de  $FE_{NO}$  y la edad, el sexo, el índice de masa corporal y los valores espirométricos no fue estadísticamente significativa.

**Palabras clave:** Óxido nítrico en aire espirado. Asma. Inflamación.

## Introduction

Asthma is a chronic inflammatory disease of the airways that leads to obstruction and bronchial hyperreactivity.<sup>1</sup> In recent years various approaches to evaluating the degree of inflammation have been investigated with a view to assessing their utility for diagnosis and monitoring.<sup>2,3</sup> One set of candidates proposed consists of markers of inflammatory activity, such as the eosinophil count in induced sputum and the fraction of exhaled nitric oxide ( $FE_{NO}$ ). We know that the synthesis of NO increases in asthma, induced by inflammatory cell activity, and that the increase can be detected in exhaled air. Studies have shown that an increase in  $FE_{NO}$  provides a sensitive indicator

of inflammation<sup>4,5</sup> and in the proper context could offer an approach to diagnosing asthma, monitoring symptoms, and verifying compliance with drug therapy as well as adjusting corticosteroid dosages.<sup>6-8</sup>

$FE_{NO}$  is measured by chemiluminescence detection. As NO reacts with ozone it produces nitrogen dioxide and when the mixture is stable, light is emitted in proportion to the concentration of NO present in exhaled air. The online method is the one most often used and it is well established in the literature.<sup>9</sup> Until recently, devices available to measure  $FE_{NO}$  have been complex, expensive, difficult to use with children, and suitable only for hospital use. Furthermore,  $FE_{NO}$  values reported in the literature have varied greatly from laboratory to laboratory. For these reasons, the NIOX-MINO (Aerocrine, Solna, Sweden) has entered the market. It offers a portable, simple, and economical way to monitor airway inflammation.

The aim of this study was to report useful information on the techniques and procedures for using the NIOX-

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MINO device and to provide reference values in comparison with measurements from the conventional chemoluminescence analyzer used in our hospital.

## Methods

### Technical Description

FE<sub>NO</sub> is usually measured in our laboratory with the N-6008 chemiluminescence sensor (SIR Madrid, Spain). In the online measurement technique recommended internationally,<sup>9</sup> the patient starts from total lung capacity and exhales at a constant rate of 50 mL/s through a mouthpiece that provides a pressure of 5 to 20 cm H<sub>2</sub>O to ensure velum closure and prevent contamination from nasal NO. The mouthpiece is fitted with a filter that reduces the concentration of ambient NO. The output is a trace that allows an initial expiratory peak to be ignored so as to measure the plateau (≥3 seconds and ≤10% variability). Three exhalations must be performed, resulting in 3 NO plateau values according to international recommendations.<sup>9</sup> The analyzer is precise to ±1% and readings have a margin for error between 0 and 500 parts per billion (ppb). The NO reading must be calibrated to 0 ppb before each test; circuits must be checked daily; the suction pump that samples air for NO analysis must be calibrated every 2 to 3 days; and carbon dioxide, flow, and volume analyzers must be calibrated every 3 to 4 months. Filters must be used and bacterial contamination checked.

The new NIOX-MINO device is a small, light, hand-held monitor measuring 24×13×10 cm and weighing 800 g. It is equipped with a sensor that detects NO by electrochemical reaction rather than by conventional chemiluminescence analysis. A main difference between the new and the traditional technique is that the patient inhales filtered air through the monitor until reaching total lung capacity; for the chemiluminescence analyzer, on the other hand, ambient air is inhaled. Next the patient exhales through the device at a flow of 50 mL/s, guided by a light and sound signal to guide and assure a steady flow. A single measurement is recommended by the manufacturer. The result is expressed on a digital display and a patient's FE<sub>NO</sub> level at different times can be saved in a memory card. The device has a lower limit of precision of 3% in measurements less than 30 ppb, of less than 10% for values over 30 ppb, and a reading range between 5 and 300 ppb. Calibration is unnecessary (Figure 1).

### Volunteers

Twenty-eight healthy non-smoker volunteers (7 males, 21 females) were chosen. All had spirometry within normal reference values, had no concurrent illnesses, and were following no regular treatments. The characteristics of the group are shown in the table.

Each volunteer began FE<sub>NO</sub> measurement in random order with either the conventional chemiluminescence analyzer (N-6008), carrying out 3 maneuvers with the online method,<sup>9</sup> or the NIOX-MINO monitor, performing a single maneuver according to the manufacturer's instructions. All measurements were always made at the same time of day, approximately 2 hours after a meal. Finally, all volunteers underwent spirometry.

### Statistical Analysis

FE<sub>NO</sub> findings were expressed as means (SD) and compared with the Mann-Whitney test. Individual results were compared with the Pearson correlation coefficient. All comparisons were bilateral and the usual level of significance of 5% ( $\alpha=0.05$ ) was



Figure 1. The NIOX-MINO monitor (Aerocrine, Solna, Sweden) for measuring fraction of exhaled nitric oxide.

used. SPSS version 11.5 software was used to carry out the analysis.

## Results

The mean FE<sub>NO</sub> reading was 20 (7) ppb (range, 8-41 ppb) with the NIOX-MINO monitor and 7 (5) ppb (range, 1-19 ppb) with the N-6008 analyzer. According to previously published NO reference values for the chemiluminescence analyzer, an abnormal FE<sub>NO</sub> level was set as 20 ppb or more<sup>10</sup> (Figure 2).

A statistically significant direct correlation between FE<sub>NO</sub> measurements from the 2 devices was detected ( $r=0.92$ ;  $P=.001$ ). FE<sub>NO</sub> readings from the NIOX-MINO device were always higher than those obtained with the N-6008. The correction indicated by linear correlation is represented by the equation  $FE_{NO} (NIOX-MINO) = 10 + [1.5 \times FE_{NO} (N-6008)]$  (Figure 3). No statistically significant correlation was found between FE<sub>NO</sub> values and age, sex, body mass index, or spirometry ( $P>.05$ ).

### Characteristics of the Study Population (n=28)\*

Age, y	35.29 (11.8)
Sex	
Men	7
Women	21
Height, cm	163.85 (7.8)
Weight, kg	67.43 (16.46)
Body mass index, kg/cm <sup>2</sup>	30.32 (14.07)
FEV <sub>1</sub> , % reference	103.57 (10.02)
FVC, % reference	137.36 (20.63)
FEV <sub>1</sub> /FVC, % reference	83.32 (7.6)

\*Data are mean (SD) or number of individuals. FEV<sub>1</sub> indicates forced expiratory volume in 1 second; FVC, forced vital capacity.

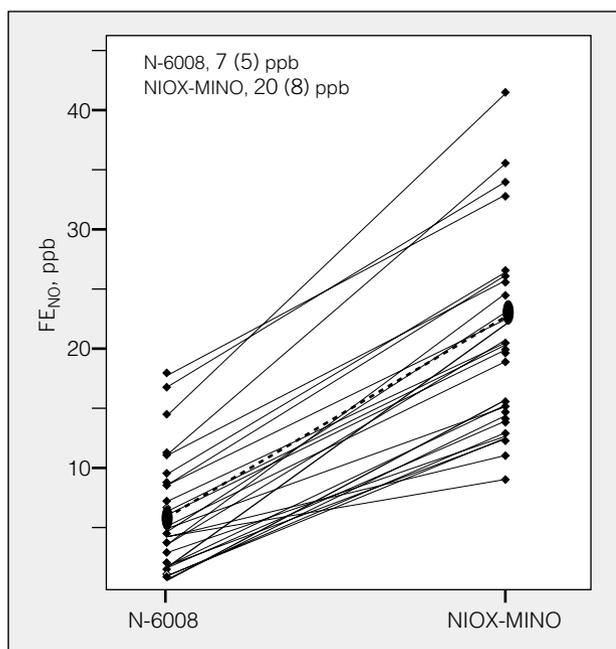


Figure 2. Comparison of fraction of exhaled nitric oxide ( $FE_{NO}$ ) measured with the N-6008 chemoluminescence analyzer (SIR, Madrid, Spain) and the hand-held NIOX-MINO device (Aerocrine, Solna, Sweden). Each volunteer's  $FE_{NO}$  measurements were higher with the NIOX-MINO device than with the N-6008 analyzer. The dotted line connects the means readings from each device; ppb indicates parts per billion.

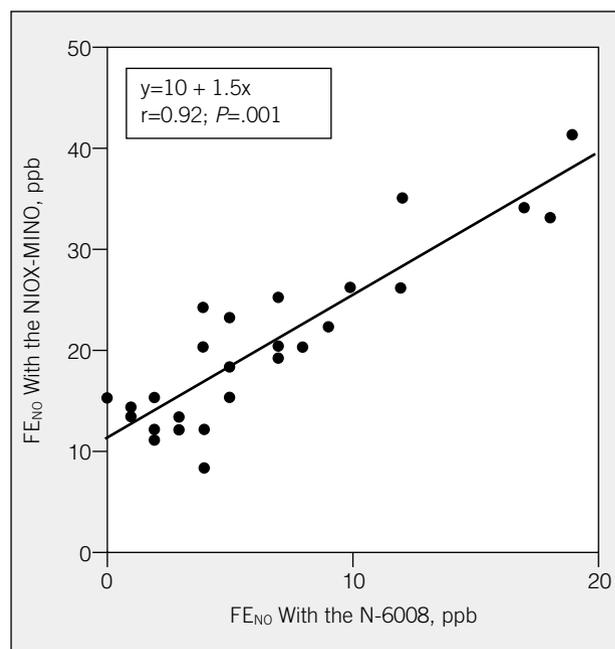


Figure 3. Correlation between fraction of exhaled nitric oxide ( $FE_{NO}$ ) measurements in healthy volunteers by the N-6008 chemiluminescence analyzer (SIR, Madrid, Spain) and the NIOX-MINO electrochemical sensor (Aerocrine, Solna, Sweden). Pearson's correlation analysis traces a regression line showing the relation between the 2 devices. The  $FE_{NO}$  level in parts per billion (ppb) measured by the NIOX-MINO monitor is plotted on the y axis;  $FE_{NO}$  measured by the N-6008 analyzer is plotted on the x axis.

## Discussion

The measurements obtained with the NIOX-MINO monitor in our clinical practice are slightly higher than those obtained with the N-6008 analyzer, a pattern that can be seen in the distribution of readings in Figure 2 (mean higher reading of 14 ppb).

There is very good correlation between  $FE_{NO}$  measurements recorded by the 2 devices, with a correction of  $\times 1.5 + 10$  for each  $FE_{NO}$  measurement obtained with the N-6008 (Figures 2 and 3), consistent with the findings of other authors.<sup>11-13</sup>

The cutoff value (mean + 2 SD) of 17 ppb for the N-6008 analyzer was within the reference values reported by other laboratories and recommended in international guidelines.<sup>9,11</sup> Likewise, the cutoff of 34 ppb for the NIOX MINO was consistent with reference values reported by other authors.<sup>12,13</sup>  $FE_{NO}$  measurement with the new NIOX MINO device is unaffected by individual anthropometric or spirometry differences, as no significant differences were found in relation to age, sex, body mass index, or spirometry, as described by other authors.<sup>11-13</sup>

An advantage of the NIOX-MINO over the chemiluminescence analyzer is that there is less risk of breath being contaminated by ambient NO.

The patient inhales through the NIOX-MINO, thus ensuring that air free of NO is taken in. In contrast, the patient inhales ambient air for the chemiluminescence analyzer.

$FE_{NO}$  can be used as a marker of inflammation in patients with inflammatory respiratory diseases like asthma, provided  $FE_{NO}$  reference values are established for each

laboratory. In this way, it is possible to obtain simple, fast and reproducible measurements for guiding better treatment of the patient.  $FE_{NO}$  is useful for clinical monitoring of treatment effectiveness and compliance. With the introduction of these new devices in the near future it will be possible to use  $FE_{NO}$  measurements to monitor asthma in the home.

A limitation of the NIOX-MINO monitor is that it does not produce a trace of the  $FE_{NO}$  curve to allow identification of a plateau corresponding to the bronchial fraction of NO (whereas the chemiluminescence analyzer does). Rather, the hand-held monitor issues a digital reading of the  $FE_{NO}$  value. As a result, the observer cannot adjust the output, possibly affecting the reproducibility of the technique. However, taking only a single measurement is advised. Other limitations derive from the respiratory maneuvers required and the possible lack of cooperation. Contraindications have not been described.

The NIOX-MINO is able to carry out 1500 measurements, each of which would cost €12. For use of the device to be cost-effective and comparable to the chemiluminescence analyzer, the manufacturer recommends performing 3000 measurements per year.

In summary,  $FE_{NO}$  measurement is a noninvasive, rapid and harmless technique that provides an inflammatory marker for studying respiratory diseases such as asthma. In the clinical setting it can allow underlying inflammation to be quantified for monitoring the patient's condition, adjusting dosages, or verifying therapeutic compliance. It can also provide an approach

to asthma diagnosis based on inflammation. Each laboratory requires reference values with its own equipment to better interpret data for this type of biological measurement. We can expect that hand-held equipment such as the NIOX-MINO described will be used in the future not only in hospital settings but also in outpatient clinics, homes, or in large-scale epidemiologic studies.

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